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SYNTHESIS OF ISOXAZOLINYLXANTHINES

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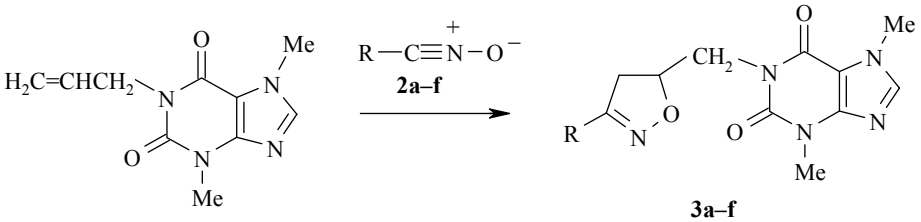
1-[5-(3-Arylisoxazolin-2-yl)methyl]-3,7-dimethylxanthines have been synthesized by the [2+3] cycloaddition of arylnitrile oxides to allyltheobromine. 7-{5-[3-(2,4-Dichlorophenyl)isoxazolin-2-yl]methyl}-1,3-dimethylxanthine was obtained by the addition of 2,4-dichlorobenzonitrile oxide to allyltheobromine. The addition of arylnitrile oxides to structural isomers of methylxanthines proceeds regioselectively with the formation of 3,5-disubstituted isoxazolines.

Keywords: allyltheobromine, allyltheophylline, arylnitrile oxides, isoxazoline.

Methylxanthines (theobromine, theophylline, caffeine) are a group of alkaloids possessing bronchodilating and lung stimulating action. Fits of uncontrolled coughing are the usual symptoms of colds, allergic reactions, and asthma. Up to the present time the most widespread agent against coughing is codeine (methylmorphine), having a limited spectrum of application due to its narcotic action. More recent investigation has shown that 3,7-dimethylxanthine (3,7-dimethyl-2,6-dioxo-3,7-dihydro-1H-purine, theobromine) is a more effective agent, not possessing the side reactions of codeine (fatigue and the risk of dependence) [1]. Consequently 3,7-dimethylxanthine is a promising compound for the synthesis of new agents against fits of uncontrolled coughing.

The isoxazoline heterocycle is also a valuable synthon for obtaining β-hydroxy ketones [2-7], γ-amino alcohols [8-10], α,β-unsaturated oximes [11, 12], and β-hydroxy nitriles [13], and its introduction into the dioxopurine molecule enables broadening of the range of synthetic derivatives of theobromine and caffeine. Compounds containing an isoxazoline fragment in the molecule also possess pharmacological activity [14-22].

The isoxazoline ring is synthesized by two routes differing in principle. These are the cycloaddition of nitrile oxides and silyl esters of a nitronic acid to an alkene or by conversion of ketone derivatives under the action of hydroxylamine. β-Chloro ketones, α,β-unsaturated ketones, and quaternary salts of Mannich bases [23] serve as starting materials in the latter reaction. The reaction is strongly dependent on pH, on the ketone:



1 **3a–f**

2, 3 **a** R = Ph, **b** R = 4-BrC_6H_4, **c** R = 2-ClC_6H_4, **d** R = 4-$Me_2NC_6H_4$, **e** R = 2,4-$Cl_2C_6H_3$, **f** R = 3,4-$(MeO)_2C_6H_3$

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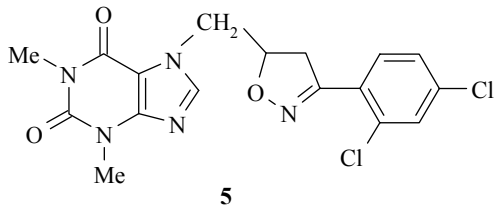
hydroxylamine ratio, and also on the substituents. Consequently a series of side products are formed in it, *viz*. oximes, dihydroxyamino ketones, hydroxyamino oximes, disubstituted hydroxylamines, dioximes, and isoxazoles. Due to this the yield of the desired compound is frequently far less than in the cycloaddition reaction.

While continuing investigations on the synthesis of compounds in which a $-CH_2-$ bridge is found between the nitrogen atom of the heterocycle and the isoxazoline ring, we have carried out a [2+3] cycloaddition of nitrile oxides **2a-f**, generated from hydroxamic chlorides in the presence of triethylamine, to N-allyltheobromine **1**.



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The corresponding 7-{5-[3-(2,4-dichlorophenyl)isoxazolin-2-yl]methyl}-1,3-dimethylxanthine **5** was obtained by the addition of 2,4-dichlorobenzonitrile oxide **4** to allyltheophylline.

The reaction was carried out in `one-pot' sequentially: 1) conversion of arylaldoxime by the action of N-chlorosuccinimide in chloroform to the corresponding hydroxamic chloride; 2) addition of the unsaturated compound; 3) addition of triethylamine as the dehydrohalogenating agent to generate the nitrile oxide. The yields of products **3a-f**, **5** were 50-83%.

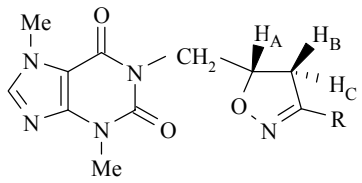
According to the data of ^{1}H NMR spectra (Table 2) the cycloaddition reaction in both cases proceeds regiospecifically with the formation of 5-heterylmethyl-substituted isoxazolines.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

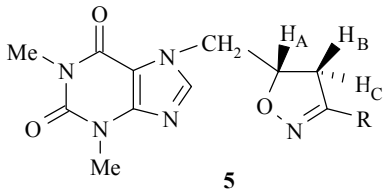
Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	Yield, %
		C	H	N		
3a	$C_{17}H_{17}N_5O_3$	60.26 / 60.17	5.01 / 5.05	20.61 / 20.64	186.5	83
3b	$C_{17}H_{16}BrN_5O_3$	47.78 / 48.82	3.80 / 3.86	16.80 / 16.74	185	74
3c	$C_{17}H_{16}ClN_5O_3$	54.80 / 54.62	4.20 / 4.31	18.32 / 18.74	163	74
3d	$C_{19}H_{22}N_6O_3$	59.33 / 59.67	5.78 / 5.80	22.06 / 21.98	233	59
3e	$C_{17}H_{15}Cl_2N_5O_3$	49.98 / 50.02	3.68 / 3.70	17.12 / 17.15	184	50
3f	$C_{19}H_{21}N_5O_5$	57.12 / 57.14	5.26 / 5.30	17.56 / 17.53	217	77
5	$C_{17}H_{15}Cl_2N_5O_3$	50.18 / 50.02	3.65 / 3.70	17.18 / 17.15	197	57

*Ethanol was the solvent for crystallization.

TABLE 2. ^{1}H NMR Spectra of Isoxazoline-containing Xanthines **3a-f** and **5**



3a–f



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Compound	Chemical shifts, δ, ppm (SSCS, *J*, Hz)
3a	3.25 (1H, dd, *J* = 7.0, *J* = 15.9, CH_C); 3.47 (1H, dd, *J* = 9.6, *J* = 15.9, CH_B); 3.54 (3H, s, CH_3); 3.96 (3H, s, CH_3); 4.09 (1H, dd, *J* = 5.6, *J* = 13.1, CH); 4.47 (1H, dd, *J* = 6.6, *J* = 13.1, CH); 5.03-5.38 (1H, m, CH_A); 7.36-7.47 (3H, m, $H_{arom.}$); 7.52 (1H, s, N=CH); 7.63–7.78 (2H, m, $H_{arom.}$)
3b	3.18 (1H, dd, *J* = 6.8, *J* = 15.4, CH_C); 3.43 (1H, dd, *J* = 9.8, *J* = 15.4, CH_B); 3.52 (3H, s, CH_3); 3.89 (3H, s, CH_3); 4.03 (1H, dd, *J* = 5.4, *J* = 13.1, CH); 4.41 (1H, dd, *J* = 7.2, *J* = 13.1, CH); 4.98-5.32 (1H, m, CH_A); 7.43 (4H, c, $H_{arom.}$); 7.49 (1H, s, N=CH)
3c	3.34 (1H, dd, *J* = 6.2, *J* = 16.2, CH_C); 3.58 (3H, s, CH_3); 3.65 (1H, dd, *J* = 9.2, *J* = 16.2, CH_B); 3.98 (3H, s, CH_3); 4.07 (1H, dd, *J* = 5.4, *J* = 13.1, CH); 4.52 (1H, dd, *J* = 7.1, *J* = 13.1, CH); 5.05-5.33 (1H, m, CH_A); 7.18-7.27 (1H, m, $H_{arom.}$); 7.29-7.43 (1H, m, $H_{arom.}$); 7.47 (1H, s, N=CH); 7.56-7.72 (1H, m, $H_{arom.}$)
3d	2.96 (6H, s, $2CH_3$); 3.14 (1H, dd, *J* = 4.6, *J* = 16.4, CH_C); 3.41 (1H, dd, *J* = 7.1, *J* = 16.4, CH_B); 3.47 (3H, s, CH_3); 3.96 (3H, s, CH_3); 3.98 (1H, dd, *J* = 5.2, *J* = 12.8, CH); 4.43 (1H, dd, *J* = 7.4, *J* = 12.8, CH); 4.92-5.23 (1H, m, CH_A); 6.67 (2H, d, *J* = 8.6, $H_{arom.}$); 7.45 (1H, s, N=CH); 7.47 (2H, d, *J* = 8.6, $H_{arom.}$)
3e	3.32 (1H, dd, *J* = 6.4, *J* = 16.8, CH_C); 3.58 (3H, s, CH_3); 3.61 (1H, dd, *J* = 9.4, *J* = 16.8, CH_B); 3.93 (3H, s, CH_3); 4.05 (1H, dd, *J* = 5.4, *J* = 13.1, CH); 4.47 (1H, dd, *J* = 7.2, *J* = 13.1, CH); 5.05-5.38 (1H, m, CH_A); 7.25 (1H, dd, *J* = 2.4, *J* = 8.2, $H_{arom.}$); 7.43 (1H, d, *J* = 2.4, $H_{arom.}$), 7.47 (1H, s, N=CH); 7.63 (1H, d, *J* = 8.2, $H_{arom.}$)
3f	3.18 (1H, dd, *J* = 4.6, *J* = 14.8, CH_C); 3.47 (1H, dd, *J* = 8.4, *J* = 14.8, CH_B); 3.58 (3H, s, CH_3); 3.92 (6H, s, $2CH_3$); 4.01 (3H, s, CH_3); 4.02 (1H, dd, *J* = 4.8, *J* = 13.4, CH); 4.47 (1H, dd, *J* = 7.2, *J* = 13.4, CH); 4.98-5.32 (1H, m, CH_A); 6.81 (1H, d, *J* = 8.1, $H_{arom.}$); 7.01 (1H, dd, *J* = 1.5, *J* = 8.1, $H_{arom.}$), 7.41 (1H, d, *J* = 1.5, $H_{arom.}$), 7.52 (1H, s, N=CH)
5	3.32 (1H, dd, *J* = 6.6, *J* = 17.4, CH_C); 3.33 (3H, s, CH_3); 3.54 (3H, s, CH_3); 3.67 (1H, dd, *J* = 9.8, *J* = 17.4, CH_B); 4.45 (1H, dd, *J* = 6.4, *J* = 13.4, CH); 4.67 (1H, dd, *J* = 3.6, *J* = 13.4, CH); 5.03-5.34 (1H, m, CH_A); 7.23 (1H, dd, *J* = 2.2, *J* = 8.4, $H_{arom.}$); 7.41 (1H, s, N=CH); 7.45 (1H, d, *J* = 8.4, $H_{arom.}$), 7.72 (1H, s, $H_{arom.}$)

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **3a-f, 5** were recorded on a Bruker WR 90 (90 MHz) instrument in $CDCl_3$, internal standard was TMS.

The general procedure for obtaining isoxazolines **3a-f, 5** is described in [25], the characteristics of the compounds obtained are given in Tables 1 and 2.

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